Remarks

After amendment, claims 40, 50-56 and 67-69 remain pending in the present application. Claims 40 has been amended to indicate that the compounds also can be administered in topical dosage form for treating cancer. Melanoma as a cancer has also been included in claim 40 given the presentation of *in vitro* data on a melanoma cell line in paragraph 30 and exhibit 3 of the attached declaration of Dr. Jack Arbiser (October, 2011). Support for the amendment to the claims can be found throughout the originally filed application and claims and in particular, for the topical dosage form, *inter alia,* on page 11, line 1, page 13, second full paragraph, page 14, first full paragraph and page 15, third full paragraph. No new matter has been added by way of this amendment.

Applicants note that any subject matter which is cancelled herein, including any subject matter canceled from previously pending claims is made *without prejudice* in order to give Applicant a chance to consider filing any one or more divisional/continuation applications to seek allowance of that subject matter.

Applicants wish to respectfully acknowledge the courtesy extended by Examiner Zarek in attending a teleconference with Applicant Arbiser and the undersigned attorney on September 15, 2011. During that teleconference, Applicant Arbiser, the undersigned attorney and Examiner Zarek discussed further evidence which could be presented which would be probative of the enablement of the presently claimed invention to place the present application in condition for allowance. The Examiner's interview summary record dated September 23, 2011 accurately describes the discussions held during that teleconference. The information which is presented in the attached Arbiser declaration and described in this response reflects those teleconference discussions.

The following evidence presented in this response and the attached Declaration of Dr. Jack Arbiser, is made to expedite allowance of the instant application and in particular, to address the enablement issue associated with the cancers that are claimed. The presently pending claims are now directed to the use of the compounds as claimed in

treating tumors and cancers as otherwise set forth in the claims. The method of treatment of the claimed tumors/cancers as set forth in the claims is consistent with the activity of the claimed compounds as anti-angiogenesis agents, both based upon experimental data in numerous cancer lines, as well as in the peer-reviewed literature, as presented in the attached Declaration of Dr. Jack Arbiser and as enclosed herewith

The accompanying declaration of Dr. Jack Arbiser is enclosed in support of the enablement of the present invention. The attached declaration outlines cell-based assays performed on benign tumor cells (FP52 SV40), malignant sarcoma cells (TSC2ang1), and melanoma cells (A375) using solenopsin to test its anti-proliferative and/or anti-cancer activity, as well as a National Cancer Institute of 60 cell lines for a variety of cancers including breast, central nervous system, colon, leukemia, melanoma, lung, ovarian, prostate and renal cancers. See paragraphs 29-31 and Exhibits 1-4 of the attached Arbiser declaration. The assays which are presented evidence that solenopsin exhibits substantial antiproliferative activity in a large number of cellular assays which is consistent with its generic use as an anticancer agent as is claimed. In addition, Applicants have presented a number of peer-reviewed papers which clearly support the experimental data that the claimed method is generic for a larger number of cancers, consistent with its anti-angiogenesis mechanism.

Objections/Rejections

The Objection to Figure 5

The Examiner has objected to originally filed Figure 5 for the reasons which are stated in the July, 2011 office action on pages 6-7. In response, Applicants have clearly indicated in the Arbiser declaration in paragraph 34 that the results for the 6 micrograms/mL test result for solenopsin (top entry) represents an artifact of the experiment conducted at that time. The artifact which occurred may be attributed to a number of factors, including but not limited to aggregation effects, solubility, sample purity, etc. As noted in the Arbiser declaration in paragraph 34, occasionally, in the SVR

assay, concentration effects have been observed. In such cases either the assay is repeated or other experiments are carried out. In this case, we have repeated this experiment several times and a more accurate experiment is presented in figure 2 of the previously submitted *Blood* 2007 paper, referenced above in paragraph 29 of the Arbiser declaration. Applicants note that they have repeated the experiment several times with the same results which are presented in figure 2 of the *Blood 2007* paper. Should the Examiner indicate the requirement to delete figure 5, Applicants will do so at the request of the Examiner.

The §112, First Paragraph Rejection

The Examiner has rejected/objected to previously pending claims 40, 50-56 and 67-69 under 35 U.S.C. §112, first paragraph as being non-enabled for tumors and cancers which are presently claimed in the instant application as stated in the office action on pages 3-6 and 7-8. In particular, the Examiner indicates that the previously pending claims are directed to the treatment of a number of tumors and cancer for which enablement of the present invention is not provided. In response, Applicants have attached the October, 2011 declaration of Dr. Jack L. Arbiser, M.D., Ph.D. in support of patentability of the present invention. Dr. Arbiser, who has extensive experience in cancer/tumor chemotherapy, provides substantial evidence that the presently claimed compounds are anti-angiogenesis inhibitors and as such, display an activity which is consistent with the generic therapy of tumors and cancer. Based upon the previously enclosed declarations of Dr. Arbiser, and the references cited therein (copies of which were submitted to the Patent Office on October 5, 2010), as well as numerous additional experiments in more than 60 cell-based assays for numerous cancers which are described herein, Applicants respectfully submit that the presently claimed invention is enabled and therefore, patentable.

The two papers previously submitted, Arbiser, et al., ***Blood***, 15 January 2007, 109, 2, 560-565 ("Blood 2007") and Park, et al., ***Journal of Infectious Diseases***, 15 October 2008, 198, 1198-201 ("Park"), evidence that the claimed compounds are

inhibitors of phosphatidyl-3-kinase (Blood 2007) and because of the small molecular size and stability of solenopsin, as evidenced by both Arbiser and Park, these characteristics make the compound amenable to topical, systemic and oral administration, and an attractive molecule for the treatment of tumors and cancer. As indicated by the combined teachings of the Arbiser and Park references, and as set forth in Dr. Arbiser's attached declaration, solenopsin thus represents close to an ideal compound for providing generic therapy against a variety of cancerous tissue and its use as an anticancer agent and is consistent with its activity as an inhibitor of angiogenesis, given that inhibitors of phosphatidyl-3-kinase activity exhibit anti-angiogenesis activity. Blood 2007, supra.

It is noted that the solenopsin compounds which are set forth in the presently claimed methods exhibit exceptional activity as inhibitors of phosphatidylinositol-3 kinase, and consequently, both directly and indirectly inhibit angiogenesis, which is critical for tumor/cancer growth and elaboration. Dr. Arbiser presents evidence in the form of two papers from his laboratory, in particular, Blood 2007 and Park, previously submitted. The first reference, Blood 2007, evidences that solenopsin is an effective inhibitor of phosphatidylinositol-3 kinase and consequently angiogenesis, and the second reference evidences that solenopsin is a stable compound and may be used consistent with its presentation as a pharmaceutical agent.

By virtue of the inhibition which is implicated in both the direct and indirect inhibition of angiogenesis and the fact that inhibition of angiogenesis is consistent with favorable therapeutic outcomes in a variety of tumors and cancer, Dr. Arbiser concludes that it is his expectation as a person of extraordinary experience and skill in cancer treatment modalities, that the present invention will be generally applicable for favorable therapeutic intervention and the treatment of a broad range of tumors and cancer as claimed. This expectation is further born out by the experimental evidence obtained from cell based assays conducted under Dr. Arbiser's supervision and control, which tested the inhibition of solenopsin on the proliferation of cells from a benign tumor (FP52 SV40), malignant sarcoma (TSC2ang1) and malignant melanoma (A395), described in the attached declaration of Dr. Arbiser, in paragraphs 29-30. In each of the assays, as

described in the Arbiser declaration, solenopsin evidenced substantial anti-proliferative activity consistent with its use as an anticancer agent as presently claimed in the present application.

In addition to the anti-cancer experiments described above, solenopsin was sent to the National Cancer Institute to determine the anti-cancer activity of solensopsin in a 60 cell-line panel. The experiments conducted by NCI are described in the attached Arbiser declaration in paragraph 31 and exhibit 4. In sum and substance, solenopsin A was tested by the National Cancer Institute (NCI) against a number of cancer cell lines. The *in vitro* testing was conducted in 60 human tumor cell lines in the following cancers: breast, central nervous system, colon, leukemia, melanoma, non-small cell lung, ovarian, prostate and renal. Pursuant to NSC guidelines, each drug (in this case, NSC 166588 (Solenopsin A) was exposed to 60 humor tumor cell lines of the various cancer cited above at five different doses for 48 hours. The results of the *in vitro* testing in the 60 cell lines is presented in attached Exhibit 4. The NCI results clearly evidenced that in virtually *all* of the tumor cell lines tested, solenopsin exhibited substantial anti-cancer activity at 1 to 100 micromolar concentrations, depending on the cell line, consistent with its use as an anti-cancer agent. All cell lines were impacted by the Solenopsin treatment, evidencing that Solenopsin exhibited anti-cancer activity against every cell line in the 60 cell-line panel. Thus, pursuant to the variety of experiments described in the Arbiser declaration, solenopsin A exhibited anti-cancer activity against a large variety of cancers in different tissues. The anti-angiogenic activity of solenopsin A is consistent with its generic use as an anti-cancer compound, the experiments presented in the Arbiser declaration are consistent with that use.

In addition to the broad-based experimental evidence which is described above and is presented in the attached Arbiser declaration, a large number of peer-reviewed literature articles also present cogent evidence which is consistent with the use of solenopsin A as a generic anti-cancer agent. This is by virtue of solenopsin's mechanism as an inhibitior of phosphatidylinositol 3-kinase, and consequently angiogenesis in tumor cells.

In particular, as set forth in the Arbiser declaration in paragraph 32, a review of the literature evidences that the inhibition of phosphatidyl inositol 3-kinase as part of an anti-angiogenesis mechanism is relevant to cancer treatment in a broad range of cancers, including skin cancer, colorectal cancer, head and neck cancer, breast cancer, including metaplastic breast cancer, lung cancer, pancreatic cancer and skin cancers, including basal cell carcinoma, squamous cell carcinoma and melanoma. In further support of this generic utility of the present invention as a treatment for numerous cancers, Applicants enclose a number of peer reviewed publications in the scientific literature which clearly evidence that inhibition of phosphatidyl inositol 3-kinase (the inhibition of the pathway through which solenopsin exhibits its generic anti-angiogenic anti-cancer effect) is consistent with cancer growth inhibition and apoptosis of cancer cells. This mechanism is shown to be important for the treatment of a number of cancers including skin cancers (Anto, et al., *The Journal of Biological Chemistry*, 278, 28, pp. 25490-25498. August, 2003, enclosed), colorectal cancer (Baba, et al., *Cancer*, April 1, 2011, pp. 1399-1408), head and neck cancer (Bian, et al., *Cancer Res.*, 2009, July 15; 69(14), pp. 5918-5926, enclosed), breast cancer (Capodanno, et al., *Human Pathology*, 2009, 40, 1408-1417 and Hennessy, et al., *Cancer Res.*, 2009, May 15, 69(10) pp. 4116-4124, enclosed), lung cancer (see Capuzzo, et al., *Journal of the National Cancer Institute*, 96, 15, August 4, 2004, pp. 1133-1141, enclosed), pancreatic cancer (Chen, et al., *Pathol. Oncol. Res.*, 2011, 17:257 pp. 257-261, enclosed), skin cancers, including melanoma, squamous cell carcinoma and basal cell carcinoma (see Jee, et al, *The Journal of Investigative Dermatology*, 119, 5, pp. 1121- 1127, 2002 and Ming, et al., *The Journal of Investigative Dermatology*, 129, pp. 2109-2112, 2009, enclosed), brain cancer (see Rong,et al., *PNAS*, 101, 52, pp. 18200-18205, December 28, 2004, enclosed) and ovarian cancer (see Wang,et al., *Oncogene*,24, 3574-3582, 2005, enclosed). These references all evidence the dramatic generic role that phosphatidyl inositol 3-kinase plays in a variety of cancers and also evidences that inhibition of this enzyme is material to the treatment of these cancers.

It is respectfully submitted that the totality of evidence presented in the attached Arbiser declaration, in the form of experimental data as well as peer-reviewed scientific publications evidences that solenopsin A is a generic anti-cancer agent useful in the presently claimed method of treating cancer of claims 40, 50-56 and 67-69. Applicants respectfully submit that the evidence presented herein, addresses the Examiner's rejection under 35 U.S.C. §112, first paragraph regarding the ability of solenopsin to treat the cancers which are set forth in the presently pending claims.

As a separate matter, Applicants have evidenced that the present application enables the present invention as it relates to making and using the invention without engaging in undue experimentation. In particular, the present specification clearly indicates the chemical compounds which are used in the present invention, provides for the syntheses of the compounds, some of which are readily available in the literature, and provides for pharmaceutical formulations which are readily prepared using known methods and pharmaceutically acceptable carriers, additives and excipients as indicated in the specification. The specification provides that effective amounts or concentrations of compounds as claimed are used in the present invention and provides, on page 15, guidelines as to the amounts or concentrations of compounds which are to be used in the pharmaceutical compositions according to the present invention. The specific disclosure in the present application, which provides for the treatment of a tumor or cancer using an effective amount of the compounds as claimed is clearly enabled. Making routine changes to the delivery of the compounds in treating a variety of cancers which rely on the generic mechanism of inhibition of angiogenesis in cancer cells and tissue to effect treatment is well within the skill of the routineer and does not amount in any way to undue experimentation. The specification, coupled with the literature cited, as well as the experimental and literature evidence presented in the attached Arbiser declaration fully support Applicants' view that their invention may be used by the person of ordinary skill without engaging in undue experimentation in conformity with 35 U.S.C. §112, first paragraph.

Based upon the attached declaration of Dr. Arbiser, the references attached thereto and the broad-based experimental evidence which is presented in the declaration, and as otherwise provided in the present application, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. §112, first paragraph.

No other rejections of the previously pending claims were made by the Examiner.

For all of the reasons which are set forth hereinabove, Applicants respectfully submit that the application is in condition for allowance and early action resulting in allowance of the instant application is earnestly solicited.

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No fee is due for the presentation of this amendment. A petition for an extension of time of two months is enclosed as is authorization to charge the petition fee of $280 to Deposit Account 04-0838 is provided. Please charge any fee due or credit any overpayment previously made to Deposit Account No. 04-0838.

Respectfully submitted,

Dated: December 5, 2011
Enclosures: Arbiser Declaration w/Exhibits;
References Cited Therein

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Certificate of Facsimile Transmission

I hereby certify that this correspondence is being sent by facsimile to Examiner Paul Zarek, in Group Art Unit 1628 of the United States Patent Office in Alexandria, VA 22313-1450 on December 5, 2011. HDC

Henry D. Coleman, Reg. No. 32,559